part drawn to a method of increasing SR-BI expression in a mammal using cDNA, or antisense; Group VI, claims 1-16, in part drawn to a method of increasing SR-BI expression in a mammal using antibodies; Group VII, claims 1-16, in part drawn to a method of increasing SR-BI expression in a mammal using SR-BI binding small molecules; and Group VIII, claims 1-16, in part drawn to a method of increasing SR-BI expression in a mammal using proteins.

The Examiner asserts that Groups I-VIII define distinct inventions "because the methods are practiced with materially different process steps for materially different purposes and each method requires a non-coextensive search because of different starting materials, process steps and goals." However, unity of invention exists where compounds included within a Markush group (1) share a common utility and (2) share a substantial structural feature disclosed as being essential to that utility. SR-BI is the principle mediator of cholesteryl ester transport from peripheral tissues to the liver and other steroidogenic tissues. The Applicant submits that the compounds of the claimed Markush group are directed to the common utility of modifying steroid production via SR-BI. The members of the claimed Markush group all share a common mechanism of action, i.e. binding a form of SR-BI. The known targeted sequence encoding SR-BI defines the complementary nature of cDNA and antisense nucleic acids, as well as the proteins, antibodies, and small molecules designed to target the SR-BI protein. The common structural feature is that they all can bind to the gene encoding SR-BI, or the SR-BI, to alter lipoprotein or cholesterol levels, and thereby steroid levels.

However, since it appears that the last amendment has created confusion as to what the invention is (a method of treatment, not a claim to the compounds that can be used to effect that

treatment), the claims have been amended to delete the language that gave rise to the eight-way restriction requirement after two and one-half years of prosecution. Support for the amendments to claim 1 are found in dependent claims 8-12, at page 7, lines 21-26, and for new claims 19-22, at page 14, lines 21-25.

To the extent the examiner requires an election of species, the applicants elect cholesterol lowering small molecules, and for the disorder, infertility.

Enablement

Much of the previous rejections in this case have centered around the alleged inability to enable one to make and use that which is claimed. In order to facilitate prosecution, and moot some of these rejections, claim 1 has been extensively amended to:

(1) refer to a method of altering fertility or treating a reproductive disorder in a mammal by

(2) administering a compound altering lipoprotein, LDL, HDL or cholesterol levels in the mammal.

The data in the application demonstrates that multiple compounds can be used to achieve this result.

Example 5, beginning at page 40, demonstrate that transient increases in SR-BI expression following administration of an adenoviral vector encoding SR-BI results in a decrease in cholesterol levels. See Table 1, page 42. Example 6, beginning at page 45, shows that SR-BI knockout animals show just the opposite – increased cholesterol levels. The females of these animals are also infertile. See page 49, lines 21-24, and example 7, page 55. Antibody blocking

studies showed similar results using antibodies to block cholesterol transport, to lower cholesterol levels, as described in example 8, beginning at page 55.

These studies clearly demonstrate that one can alter fertility, as defined by the claims, by altering cholesterol levels.

Enclosed is a recent paper by the inventors which provides still further evidence that the claimed method is enabled, as described in the application. See the enclosed article by Miettinen, et al., J. Clin. Invest. 108:1717-1722 (2001). The data in this article demonstrates restoration of fertility in the SR-BI knockout mice described in examples 6 and 7 by administering probucal. Probucal, 4,4'-(isopropylidene-dithio)-bis-(2,6-di-tert-butylphenol), is a cholesterol lowering drug.

Favorable consideration of claims 1-16 and 19-22 is therefore earnestly solicited.

Respectfully submitted,

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APPENDIX: Marked up Claims as Amended

1. (Four times amended) A method for [modifying steroid production] altering fertility or treating a reproductive disorder in a mammal [in need of treatment by alteration of reproductive hormone levels] comprising

administering a compound [directly inhibiting SR-BI function or expression or a compound selectively increasing expression of SR-BI thereby directly resulting in the selective alteration of cholesterol or cholesteryl ester from high density lipoprotein or other lipoproteins by specifically altering expression of or binding to cholesterol or cholesteryl ester of SR-BI to steroidogenic tissues producing reproductive hormones, wherein the compound is selected from the group consisting of SR-BI cDNA, SR-BI anti-sense nucleic acids, SR-BI antibodies, and SR-BI receptor binding small molecules or proteins] altering lipoprotein, LDL, HDL or cholesterol levels in the mammal.

2. The method of claim 1 wherein the compound alters SR-BI expression in the tissue.

3. The method of claim 1 wherein the compound alters binding of SR-BI to high density lipoprotein including cholesteryl ester or other lipoproteins.

4. The method of claim 2 wherein the compound decreases SR-BI expression in the tissue.

5. The method of claim 2 wherein the compound increases SR-BI expression in the tissue.

6. The method of claim 3 wherein the compound decreases SR-BI binding to lipoprotein or transfer of cholesteryl ester in the tissue.

7. The method of claim 3 wherein the compound increases SR-BI binding to lipoprotein or transfer of cholesteryl ester in the tissue.

8. The method of claim 1 wherein the mammal is a female and the compound is administered in an amount effective to prevent normal reproductive function.

9. The method of claim 1 wherein the mammal has a disorder characterized by overproduction of steroids.

10. The method of claim 1 wherein the mammal has a disorder characterized by underproduction of steroids.

11. The method of claim 10 wherein the disorder is menopause.

12. The method of claim 1 wherein the mammal has a disorder which can be treated by decreasing production of steroids.

13. The method of claim 12 wherein the disorder is breast or prostate cancer.

14. The method of claim 12 wherein the disorder is endometriosis or fibroid tumors.

15. The method of claim 1 wherein the compound differentially alters the activity of, or expression of, SR-BI in different tissues.

16. The method of claim 11 wherein the compound increases SR-BI expression in reproductive tissues and decreases or does not increase SR-BI expression in liver.

Please add new claims 19-22.

19. The method of claim 1 wherein the compound is an antibody to SR-BI.

20. The method of claim 1 wherein the compound is a drug that decreases production of steroids via selective binding to SR-BI.

21. The method of claim 20 wherein the compound decreases cholesterol levels to decrease steroid levels.

22. The method of claim 21 wherein the compound inhibits cholesterol transport.

APPENDIX: Clean Copy of Claims

1. (Four times amended) A method for altering fertility or treating a reproductive disorder in a mammal comprising

administering a compound altering lipoprotein, LDL, HDL or cholesterol levels in the mammal.

2. The method of claim 1 wherein the compound alters SR-BI expression in the tissue.

3. The method of claim 1 wherein the compound alters binding of SR-BI to high density lipoprotein including cholesteryl ester or other lipoproteins.

4. The method of claim 2 wherein the compound decreases SR-BI expression in the tissue.

5. The method of claim 2 wherein the compound increases SR-BI expression in the tissue.

6. The method of claim 3 wherein the compound decreases SR-BI binding to lipoprotein or transfer of cholesteryl ester in the tissue.

7. The method of claim 3 wherein the compound increases SR-BI binding to lipoprotein or transfer of cholesteryl ester in the tissue.

8. The method of claim 1 wherein the mammal is a female and the compound is administered in an amount effective to prevent normal reproductive function.

9. The method of claim 1 wherein the mammal has a disorder characterized by overproduction of steroids.

10. The method of claim 1 wherein the mammal has a disorder characterized by underproduction of steroids.

11. The method of claim 10 wherein the disorder is menopause.

12. The method of claim 1 wherein the mammal has a disorder which can be treated by decreasing production of steroids.

13. The method of claim 12 wherein the disorder is breast or prostate cancer.

14. The method of claim 12 wherein the disorder is endometriosis or fibroid tumors.

15. The method of claim 1 wherein the compound differentially alters the activity of, or expression of, SR-BI in different tissues.

16. The method of claim 11 wherein the compound increases SR-BI expression in reproductive tissues and decreases or does not increase SR-BI expression in liver.

19. The method of claim 1 wherein the compound is an antibody to SR-BI.

20. The method of claim 1 wherein the compound is a drug that decreases production of steroids via selective binding to SR-BI.

21. The method of claim 20 wherein the compound decreases cholesterol levels to decrease steroid levels.

22. The method of claim 21 wherein the compound inhibits cholesterol transport.